REMARKS

I. Claims in the Case

Claims 19-30 are pending and under examination. Claims 1-18 are canceled. Claim 23 is currently amended to correct a typographical error, and no claims have been added.

II. Sequence Requirements

The Action states the Applicant has failed to comply with requirements of the sequence rules, and specifically directs attention to pages 68 and 69 of the Specification. The Action further states that the Office may hold the Applicant non-responsive due to a failure to comply. In response, Applicant notes that a preliminary amendment filed concurrently with the Application on March 16, 2004 amends pages 68 and 69 of the Specification thereby appending the SEQ ID NOs. to all mention of specific sequences on those pages. Preliminary Amendment, p.2 ¶6. Thus, Applicant's Specification has been in compliance since filing, and removal of this objection is respectfully requested.

III. Priority Information

The Action states the Applicant has failed to update the priority information required by the Office Action mailed 4/12/07, and that such update may be conducted by amendment to the Specification or an ADS. The Action further states that the Office may hold the Applicant non-responsive due to a failure to comply. In response, Applicant notes that an ADS was filed concurrently with the Application on March 16, 2004 that amends the Specification thereby updating the priority information. ADS, p.2 ¶6. Applicant further notes that this document is not titled "Application Data Sheet," as is required under the current version of 37 C.F.R § 1.76, however, this requirement was added after the document was filed. Fed. Reg. 56507 Vol. 69 No.

182, column 2 (Tuesday, September 21, 2004). Thus, Applicant's Specification has been in compliance since filing, and removal of this objection is respectfully requested.

Regarding the Action's understanding of the priority entitlements of different aspects of Applicant's invention, as it is not relevant to Applicant's response, Applicant neither agrees nor disagrees with the assertions stated therein. Applicant will take a position if and when it becomes necessary.

IV. Claim Rejections -- §112, second paragraph

The Final Action states claims 19-30 are rejected as indefinite under 35 U.S.C. §112, second paragraph, however, only claims 20, 24 and 30 are specifically noted as unclear. The Action asserts it is unclear as to whether the amount administered is in units or international units, and whether the dosage administered is per kg or total dose administered, in these claims. Applicant respectfully traverses as follows:

The claims as recited above are not indefinite because their meaning is discernable when construed under correct principles, including: (A) the content of the particular application disclosure; (B) the teachings of the prior art; and (C) the claim interpretation that would be given by one possessing the ordinary level of skill in the pertinent art at the time the invention was made. M.P.E.P. § 2173.02. AS fully explained below, when properly construed, it is clear that claims 20, 24, and 30 refer to total dosage in international units (I.U.).

Applicant's Specification recites that generally, interferon can be administered per the invention at a dosage of, "from about 50 I.U./kg to about 25000 I.U./kg," on page 21 lines 14-15. Positive results were achieved when individual humans (regardless of kg per individual) each ingested 30,000 units total dosage of IFN-α. Specification, p.8 ll. 2-4; p.13 ll. 9-19. Also

described is the rough equivalent dosage of 30,000 units for a 60 kg human to 10 units for a 20 mg mouse. *Id.*, p.56 ll.13-19.

Additionally, Applicant notes that it is customary in the art to refer to interferon in terms of International Units ("I.U.") U.S. Patent Nos. 5,019,382 col. 3 ll. 45-52; 4,497,795 col. 4 ll. 59-63 (explaining the custom in the art and setting forth a meaning for the term "unit" specific only to those particular disclosed inventions and utilizing the specific VSV virus), both cited by the Action. Further, claims 20, 24 and 30 each depend from claims that set forth the claimed dosage as about 50 I.U./kg to about 25,000 I.U./kg. There is no reason, then that a person of skill in the art would interpret "units" referred to in dependent claims as anything other than "international units," as referred to in the independent claims.

In contrast, implementing the Action's suggested construction that 30,000 units might refer to 30,000 units/kg would result in improper dependent claims, each claiming a dosage outside the range recited in the independent claims 19, 23, and 36. Thus, one of skill in the art would understand that total dosage is referred to in claims 20, 24, and 30. In light of the above, Applicant submits that the claims are definite and discernable when properly analyzed. M.P.E.P. § 2173.02. Removal of the rejection is thus respectfully requested.

V. Claim Rejections -- §112, first paragraph

The Action states that the Specification is enabling for (1) treating destructive joint disease associated with rheumatoid arthritis in an individual, (2) reducing inflammation associated with rheumatoid arthritis in an individual, and (3) reducing the level of interleukin in an individual with rheumatoid arthritis by oral administration of IFNα. However, the Action rejects claims 19-22 for lack of enablement under 35 U.S.C. §112, first paragraph, asserting that use of oral IFNα to prevent destructive joint disease associated with rheumatoid arthritis in an

individual is not enabled by the Specification. Specifically, the Action asserts that the minimal requirement of providing reasons for uncertainty of enablement is met per *In re Bowen*, 492 F.2d 859, 862-63 181 USPQ 48, 51 (CCPA 1974), that the Shiozawa *et al.* (1992) ("Shiozawa") reference and absence of guidance regarding patient selection and disease symptoms, provide a reason to question enablement, particularly in light of the nature of the invention. Final Action, p.4-6. Applicant respectfully traverses as follows.

The M.P.E.P. Requires a Reasonable, Sufficient Basis for Questioning Enablement

The M.P.E.P § 2164.04 discusses ***all*** of the following regarding the subject and title of the section, "Burden on the Examiner Under the Enablement Requirement." At a minimum when making an enablement rejection, reasons (*i.e.* a basis) for the uncertainty of the enablement must be provided. *In re Bowen*, 492 F.2d 859, 862-63 181 USPQ 48, 51 (CCPA 1974). However, that reason or basis must be sufficient and reasonable. "The examiner has the initial burden to establish a ***reasonable basis*** to question the enablement provided...." *In re Wright*, 999 F.2d 1557, 1562, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993) (emphasis added). A proper rejection for failure to teach how to make and/or use is made when there is ***sufficient reason*** to doubt the statements in the specification that are relied upon for enabling support. *In re Marzocchi*, 439 F.2d 220, 224, 169 USPQ 367, 370 (CCPA 1971). The Patent Office must back up its assertions with acceptable evidence or reasoning. *Id.* "[S]pecific, technical reasons are always required." M.P.E.P § 2164.04. Thus, the burden is not discharged by providing "reasons," when as here, they are neither sufficient nor reasonable, and neither specific nor technical.

What Shiozawa Does Not Teach Is Not Evidence of Non-enablement

The Final Action states that the Shiozawa reference establishes a reasonable basis to question enablement because it teaches treatment of rheumatoid arthritis but not the prevention

of destructive joint disease. Final Action, p.5. Assuming without agreeing that this is a true characterization of Shiozawa, this position must fail because it depends entirely upon what a reference ***does not teach***. If this logic is carried forward, it means that any reference that does not teach an aspect of an applicant's invention, indicating it may have probative value under 35 U.S.C. §§ 102 or 103, automatically also provides a basis to question enablement under 35 U.S.C. § 112. Specific to the instant facts, this logic means that because Shiozawa makes absolutely no mention of destructive joint disease, this is sufficient and reasonable basis to question whether Applicant's invention could have prevented destructive joint disease. This "absence" in the prior art cannot possibly provide the ***required specific and technical reasons*** for doubting enablement of this aspect of Applicant's invention, thus the burden is not met. M.P.E.P. § 2164.04

Only the Claimed Invention Must be Enabled

Additionally, the Action also argues that no patient population selected for preventing destructive joint disease is identified in the Specification, and if a patient population was identified that has disease symptoms, then the onset of the disease has taken place, thus the disease cannot be prevented, only further progression slowed or stopped. Final Action, p.5. Yet, this argument also provides no basis to question enablement, and shows an apparent misunderstanding of Applicant's invention, specifically, the difference between destructive joint disease and rheumatoid arthritis ("RA"). RA patients can be identified that do not have destructive joint disease, and only prevention of destructive joint disease as claimed need be enabled. M.P.E.P. § 2164 ("The invention that one skilled in the art must be enabled to make and use is that defined by the claim(s) of the particular application or patent.").

Specifically, Example 37 explains that a certain fraction of RA patients will develop destructive joint disease. Specification, p.85 ll. 17-19. Prevention of the destructive phase of RA in a non-toxic, patient-acceptable method was a goal of oral IFN-α therapy. *Id.*, p.85 ll. 19-23. Similarly, claim 1 is for, "a method of preventing ***destructive joint disease associated with rheumatoid arthritis*** in a human individual ***with an earlier stage of rheumatoid arthritis***...," (emphasis added). "Early treatment of RA with ingested IFN-α prevents or retards progression of RA...," Specification, p.86 ll. 11-13. Thus, Applicant has clearly identified a target patient population in the Claims as well as the Specification. Further, the above makes clear that not all RA patients have or will develop destructive joint disease, other phases (besides destructive) of RA exist, and at least some phases or stages of RA occur before the onset of destructive joint disease.

The Specification therefore teaches a patient having early stage rheumatoid arthritis but not suffering from destructive joint disease could be identified (*e.g.* by the ACR criteria for diagnosis of RA; Example 36) and treated with IFN-α to prevent the destructive phase from ever occurring. In view of this distinction between destructive joint disease and RA, and identification of potential patients ***in the claims***, Applicant submits that no reason for questioning enablement on this basis exist and the Examiner's burden is clearly not met.

Adequate Examples and Guidance Are Provided

Furthermore, Example 36 demonstrates the results of an open label phase I study of orally ingested IFN-α in the treatment of patients with clinically stable RA, and the compilation of results in Table 2 show that in 3 of the 4 patients treated there was substantial improvement in clinical disease indicia. Next, Example 37 describes "a trend toward inhibition of CD3- and Con A-mediated IL-1, IL-6, and IL-8 secretion after eight weeks," of treatment with orally ingested

IFNα. Specification, p.84 ll.6-9. Considering a reduction of inflammatory cytokine production can prevent progression of RA, Example 37 clearly provides enabling support for Applicant's claims. *Id.*, p.85 ll. 2-16; p.86 ll. 11-13. One of skill in the art need only apply the teaching in Examples 36 and 37 specifically to early stage RA patients to practice the invention. Thus, Applicant has provided sufficient examples, guidance, and direction to enable the invention without undue experimentation. M.P.E.P. § 2164.01(a).

For the foregoing reasons, Applicant submits the claims are enabled and respectfully requests withdrawal of the rejection of claims 19-22 for lack of enablement under 35 U.S.C. §112, first paragraph.

VI. Claim Rejections – 35 U.S.C. §103

The Action rejects claims 19-26 as obvious over the combination of Shiozawa *et al.* ("Shiozawa") in view of Cummings, U.S. Patent No. 4,497,795 ('795) and Cummings U.S. Patent No. 5,019,382 ('382), and claims 27-30 as obvious over the combination of references above, further in view of Aman *et al.* ("Aman"). Specifically, the Final Action states that Shiozawa teaches administering IFN-α to treat rheumatoid arthritis, which allegedly will inherently treat destructive joint disease associated with rheumatoid arthritis; the '795 patent teaches oral administration and dosage; the '382 patent teaches conversion from I.U.to "units;" and that the elements are expected to perform their expected functions to achieve their expected results when combined for a common known purpose. Final Action, p.6-8. Aman is cited for teaching the reduction of interleukin-1 after interferon administration. Non-final Action dated 4/12/2007, p.9. Applicant respectfully traverses as follows.

After a determination of the scope and contents of the prior art, a comparison of the differences between the prior art and the claims at issue, and a resolution of the level of ordinary

skill in the art, the Action fails to show the claims are *prima facie* obvious in view of the prior art because (1) the gap between the prior art and Applicant's claim limitations has not been bridged, and (2) no proper rationale to support an obviousness rejection is presented. M.P.E.P. § 2143.03; *Dann v. Johnston*, 425 U.S. 219, 230, 189 USPQ 257, 261 (1976).; Examination Guidelines for Determining Obviousness Under 35 U.S.C. 103 in View of the Supreme Court Decision in *KSR International Co v. Teleflex Inc.*, 72 Fed. Reg. 57,526 (Oct 10, 2007); *Graham v. John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966); *KSR Int'l Co. v. Teleflex Inc.*, 550 U. S. ____, 127 S. Ct. 1727, 1741 (2007).

The Prior Art Does Not Teach The Elements of Applicant's Claims

The Final Action concedes that Shiozawa, "does not teach the prevention of destructive joint disease...." Final Action, p. 7. In comparison, claim 19 ***claims a method of preventing destructive joint disease*** associated with rheumatoid arthritis in a human ***with an earlier stage of rheumatoid arthritis***. Thus, the teaching of Shiowaza appears irrelevant. M.P.E.P. §2143.03 ("All words in a claim must be considered in judging the patentability of that claim against the prior art," citing *In re Wilson*, 424 F.2d 1382, 1385, 165 USPQ 494, 496 (CCPA 1970)). The Final Action also states that treatment of rheumatoid arthritis as described by Shiozawa will inherently treat destructive joint disease, however, this assumption is not true. As described above, Example 37 explains that only a certain proportion of RA patients will develop destructive joint disease. Specification, p.85 ll. 17-19. Thus, treatment of rheumatoid arthritis does not *de facto* treat destructive joint disease because not all patients with the former will develop the latter. Further, Shiozawa does not disclose destructive joint disease, a destructive phase of RA, or that recognized phases/stages of the disease exist. As a result, Shiowaza cannot

be said to address the requirement in Applicant's claim 19 that the preventative treatment be given to a patient with an earlier stage of RA.

It is also uncontested that Shiozawa teaches administration of IFN-α only by intramuscular administration, and says nothing about whether RA is amenable to therapy by oral IFN-α, and certainly nothing about what oral dosage would be effective. Although the Final Action states that oral administration and dosage are taught by the '795 patent while the '382 patent teaches conversion of international units to units, regarding the '382 patent, the conversion taught therein is relevant only to ***that*** particular invention and has no relevance to ***Applicant's***. As for the '795 patent, it teaches low doses of orally administered interferon can stimulate the appetite of chickens, cows, pigs, and guinea pigs. *See* Examples, '795 patent. However, oral administration to humans is not taught, dosage for humans is not taught, and treatment of rheumatoid arthritis and/or related conditions is not taught. Further, the '795 patent explains that at the time, it was believed that the mammalian digestive environment would destroy interferon biological activity, and interferon administration for cancer therapy in humans caused terrible side effects including loss of appetite. '795 patent, col. 3 ll. 1-2 and ll. 3 2-36.

Thus, the '795 patent does not teach or suggest oral administration of interferon to humans with RA, and in fact indicates it may not work in certain digestive systems (plus a gizzard and/or ruminant system hardly correlates to human digestion). The '795 also describes interferon administered to humans has side effects that may result in the opposite of the intended effect. Similarly, Aman teaches the effect of IFN-α on bone marrow tissue cultures, including reduced IL-1B. Yet, a phenomenon reported in healthy tissue cultures that are directly treated with a compound cannot be said to teach a drug therapy or dosage to humans suffering from rheumatoid arthritis that swallow their treatment. Accordingly, no where in the cited references

is oral administration of IFN-α to humans, or *in vivo* reduction of interleukin, taught or suggested. The Final Action characterizes Applicant's position as arguing the references individually. This is not the case; Applicant is simply taking into consideration ***all words in the claims, as is required.*** M.P.E.P. § 2143.03.

No Proper Rationale Supporting Obviousness if Provided

The Supreme Court has held that demonstrating the several claimed elements exist in the prior art is insufficient to find obviousness, rather, reasons for prompting a person of skill in the art to combine those claimed elements in the claimed fashion must be identified. *KSR*, 127 S. Ct. at 1741. Thus, assuming *arguendo* that the elements of Applicant's claims are taught in the prior art, or the gap between the prior art and the claims can be readily bridged by one of skill in the art, the burden of showing *prima facie* obviousness is nonetheless not met. M.P.E.P. § 2142 ("The initial burden is on the examiner to provide some suggestion of the desirability of doing what the inventor has done.").

The Final Action cites M.P.E.P. § 2144.07 and states that the "prior art elements are expected to perform their expected functions to achieve their expected results when combined for a common known purpose." Yet, no correlation of what element is supposedly performing what function resulting in what expected result, is provided. Further, the M.P.E.P. recognizes that some degree of predictability such that an expectation of success is reasonable, is required when a proper rationale for finding obviousness is applied. M.P.E.P. § 2143.02. The required degree is simply not present here.

Specifically, the '382 patent together with the '795 patent teach that the appropriate dosages of oral IFNα vary dramatically depending on the disease being treated. The '795 patent, as pointed out by the Examiner, teaches use from 500 to 5000 IU/Kg to stimulae appetite in

animals; the '382 patent, in contrast, teaches use of 0.01 to about 5 I.U. of IFN-α per lb (0.02 to about 11 I.U. IFN-α per kg) to treat various diseases and disorders including RA. This dosage is ***substantially*** lower that the dosage found by the present inventors to be efficacious in the treatment of RA, ***teaches a high limit that is nearly five times lower that Applicant's low limit***, and certainly ***does not overlap***. MPEP § 2144.05. Thus, this is not at all like the *Peterson* or *Aller* cases cited in the Actions, as in those cases the issue was optimization within, or very close to, a disclosed range. *Id.*

The differences may well be attributable to the fact that the '382 patent is teaching a different method of administration from that claimed here – the '382 patent teaches simply to contact the oral mucosa with the IFNα, and does not teach or suggest "immediately swallowing" as required by the present claims. And although the Final Action states that oral administration and dosage are taught solely by the '795 patent, once again, the ranges do not overlap. Further, as discussed above, the '795 patent teaches dosages for appetite modulation ***only***, does not teach or suggest oral administration of interferon to humans with RA, indicates it may not work in certain digestive systems, and teaches side effects in humans that may result in the opposite effect than intended. Considering the vast change in scale for dosage in the '382 patent compared to Applicant's claims, the differences in disease and species treated in the '795 patent compared to Applicant's claims, and contrary teachings regarding oral administration and interferon side effects in humans, the requisite level of predictable results and expectation of success is absent. Thus, there is no proper reasoned basis justifying the legal conclusion of obviousness of claims 19-26. "Rejections on obviousness grounds cannot be sustained by mere conclusory statements; instead, there must be some articulated reasoning with some rational

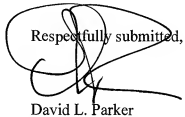
underpinning to support the legal conclusion of obviousness." *KSR Int'l Co. v. Teleflex Inc.*, 127 S. Ct. at 1741.

For all the reasons just stated above, no proper rationale supporting obviousness is provided for claims 27-30, despite the inclusion of Aman. Aman is cited for teaching the reduction of interleukin-1 after interferon administration, but Aman's teaching is limited to bone marrow tissue cultures to which interferon is directly applied at a dosage of 1000 U/mL. How this might correlate to intact organisms, and in particular humans, is unknown, and Aman states that the biological importance of the observed IFN-α action *in vivo* is unclear. Aman, p.4148 col. 2 ¶3. Thus, Aman admits the limits of its teaching, and the requisite level of predictable results and expectation of success needed to support an obviousness rejection of claims 27-30 is lacking.

Applicant has shown above that claims 19-26 are not obvious over the combination of Shiozawa in view of Cummings, '795 and Cummings '382, and claims 27-30 are not obvious over the combination of those references in further view of Aman. Removal of the rejection of all claims under 35 U.S.C. § 103 is thus respectfully requested.

VII. Conclusion

It is submitted that the foregoing response is a complete response to the outstanding official action, and that the case is now in condition for allowance. The Examiner is invited to contact the undersigned attorney at (512) 536-3055 with any questions, comments or suggestions relating to the referenced patent application.



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